Universidade de Lisboa

Faculdade de Farmácia

Tablet subdivision

Assessment of compliance with regulatory requirements of medicines marketed in Portugal

Andreia Filipa Bragança Paisana

Mestrado Integrado em Ciências Farmacêuticas

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Trabalho de Campo de Mestrado Integrado em Ciências Farmacêuticas apresentado à Universidade de Lisboa através da Faculdade de Farmácia

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Resumo

Introdução e Objetivos: O objetivo deste estudo foi determinar se os comprimidos com ranhura de divisão, comercializados em Portugal, apresentam uma quebra deficiente e se tal se constitui um obstáculo, nomeadamente para a população idosa. Outro objetivo foi avaliar a conformidade deste tipo de comprimidos com os requisitos regulamentares e identificar possíveis incoerências relacionadas com a rotulagem.

Métodos: Foi realizado um estudo com 47 voluntários, de modo a avaliar se a perda de massa durante a subdivisão de comprimidos é significativa e para quantificar a facilidade de quebra de comprimidos para os utentes. Foram incluídos comprimidos "padrão" em cada conjunto dado aos voluntários. Esperava-se que os utentes manifestassem o grau de dificuldade de quebra de modo a ser detetada a quota parte atribuivel a cada utente em si. Antes dos conjuntos serem cedidos aos utentes foram avaliados em laboratório em termos de uniformidade da massa, bem como da resistência ao esmagamento (dureza dos comprimidos) e as dimensões dos mesmos. Esperava-se que estes testes apresentassem resultados relativamente ao desvio de massa e que os mesmos, em conjunto com as características dos comprimidos ajudassem a prever o comportamento dos mesmos no estudo com os voluntários.

Resultados: Em cerca de 10% das observações verificou-se a incapacidade dos voluntários em quebrar os comprimidos ou a sua fragmentação em mais do que as duas metades esperadas. Em cerca de metade das avaliações os utentes classificaram os comprimidos como muito fáceis de quebrar. No entanto, num quinto das observações os utentes avaliaram os comprimidos como difíceis ou muito difíceis de quebrar, bem como os casos em que o utente não conseguiu partir o comprimido.

Conclusão: A implementação de requisitos regulamentares é de extrema importância, pois critérios mais rigorosos permitirão um menor número de não conformidades e, portanto, maior segurança para o utente em relação ao uso de comprimidos com ranhura de quebra. O uso de modelos de previsão pode ser um recurso útil que permita determinar quais os parâmetros físicos e farmacotécnicos que devem ser otimizados de modo a ser obtida uma subdivisão mais precisa e adequada de comprimidos ranhurados.

Palavras-chave: divisão de comprimidos; comprimidos com ranhura; facilidade de quebra; divisibilidade de comprimidos; aspetos regulamentares.

Abstract

Introduction & Aims: The aim of this project was to determine if the tablets bearing a break or score line, marketed in Portugal, present inaccurate subdivision, especially regarding the elderly population. Another aim was to assess the compliance with regulatory requirements of such products, and to target possible issues regarding labelling.

Methods: A study comprehending 47 volunteers was performed, to evaluate if mass loss during tablet subdivision is significant and to quantify the ease of subdivision of tablets for the patients. Standard tablets that would be considered either too hard or two easy to break were included in each set given to the volunteers, in order to detect possible patient-related issues. Previously to this study, the mass uniformity of the provided tablets was assessed, as well as the resistance to crushing (tablet hardness) and measurements of the tablets. It was expected that assessments presented mass deviation results and tablet characteristics that would help to predict the behavior of the tablets in the study with the volunteers, as well as an established prediction model.

Results: About 10% of the observations reflect either the inability of the volunteers to break the tablets or the splitting of tablets in more fragments than the two expected halves. Around half of the observations correspond to situations in which the patients classified the tablets as very easy to break. However a fifth of the observations represent situations where the patients found the tablets hard or very hard to break as well as cases where the patient was not able to break the tablet.

Conclusion: Implementation of regulatory requirements have a particular importance since more strict criteria would allow less non conformities, and therefore more safety for the patient regarding the use of scored tablets. The use of prediction models can be used as an asset in order to determine which tablet physical and pharmacotechnic parameters should be optimized for an enhanced and accurate tablet subdivision.

Keywords: tablet subdivision; scored tablets; breakability of tablets; splitability of tablets; regulatory requirements.

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Abbreviations

EMA	European Medicines Agency
FDA	Food and Drug Administration
INFARMED	National Authority of Medicines and Health Products, I.P.
Ph. Eur.	European Pharmacopoeia
PIL	Product Information Leaflet
RLD	Reference Listed Drug
SmPC	Summary of Product Characteristics
USP	United States Pharmacopeia
WHO	World Health Organization

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1 Introduction

1.1 Usage of scores to break tablets

1.1.1 The aim of tablet score lines

Patients split tablet for various reasons, namely for adjusting the dosage (1) because the dosage that they need is not marketed (2) or if the dosage is marketed but it is unavailable. Splitting tablets is also a solution if the tablet is too big for the patient to swallow so they break it in half to ease the swallowing of the tablet. (3) There is also a third cause, when two tablet strengths have the same cost, then splitting leads to the cost of treatment becoming cheaper. (4)(5) What can also occur regarding the price is that a higher strength can represent a larger reimbursement. (6)

Tablet subdivision allows dose flexibility across specific population – as the paediatric and the elderly. (3) For example, in case of need to titration or to reduce side effects. (2) (5)

1.1.2 Issues of tablet subdivision

When a patient breaks a tablet in two halves, they can break unevenly. Also, the patient can experience cases of mass loss, them being crumbling and powdering. (2) (7) This has a particular impact in drugs with a short therapeutic margin, due to mass loss. (2) Patients relate the inaccurate subdivision of tablets with quality issues, leading to non compliance to medication by the patient. (5)

Another problem with subdivision is that it entails that the drug is removed from the foil blister, therefore exposing it to air and humidity, increasing the rate of degradation, an in consequence adverse effects may appear because of these

degradation products. Thus it should be taken in account for how long are the tablets left split. (2)

Another unwanted case that can occur is that if a tablet which is coated with the purpose of masking the unpleasant taste of the drug that it contains, than the flavour related masking effect is disrupted because of splitting it. (2) Also regarding coating, Toxicity effects can occur if the enteric coating is disrupted, due to the drug included in such tablet being irritant. This can also happen with antineoplastic drugs, since they can lead to intoxication. (8)

Apart from the issues with scored tablets, an even greater problem is that tablets that are not scored are also subdivided, sometimes advised from the prescriber, reflecting lack of information by healthcare professionals. (6)

1.1.3 Causes to uneven splitability and mass loss

1.1.3.1 Related to the patient

There are a few patient's characteristics that can handicap tablet splitability - specially because of age progression - namely visual acuity, dexterity and strenght. (4) Some diseases that the elderly present more commonly as Parkinson's disease and arthritis, can also influence the splitability (7), since they reduce grip strength and cause impaired manual dexterity. (2)

Even though there are various methods for tablet splitting - namely the usage of hands, knives or tablet cutters - even the usage of tablet cutters imply some level of dexterity. (2) So outcomes of tablet scoring depend not only on the user but also on the device. (5)

There also might be some compliance issues regarding the elderly, who sometimes skip or double the doses not to break the tablets. Also sometimes they retain broken halves that were not used, thus it is advised to instruct patients about the appropriate way to store tablet halves. (2)

It is also reported that sometimes patients break tablets by their own choice, which can lead to problems if they are not well informed. (6)

1.1.3.2 Related to tablet characteristics

With or without score marks, the size, the shape (4)(7) and the hardness (3) of a tablet can affect the accuracy of cutting it in half. If the tablet is too small, has an

irregular shape or is only scored in one side, it can also lead to inaccuracy of splitting. (2)

A study that aimed to develop a model to predict the ease of subdivision based on physical characteristics of tablets established which of these characteristics would be crucial for either round or oblong tablets. For both types of tablets, the diameter and the resistance to crushing have significance. For oblong tablets also the ratio between diameter and width has importance as does the depth of the score line. In the case of round tablets it also matters if they are scored in either only one side of the tablet or both sides and if the tablet is either flat or biconvex. (9)

Techniques as compress molding and multi-layered tablets improve tablet scoring accuracy. (3) Pressure sensitive tablets are also an alternative that aid the subdivision. (7) An example of a pressure sensitive tablet and the proper way to break it is shown in **Figure 1**. (10)

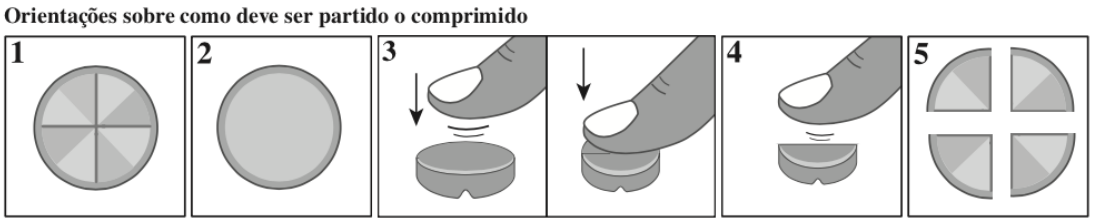

Figure 1. Pressure sensitive tablet
Retrieved from (10)

1.2 Regulatory requirements and Guidance documents

1.2.1 The European Pharmacopeia (Ph. Eur.) approach

The Ph. Eur. established for the first time Pharmacopeial standards regarding tablet subdivision, in 2002. Since then these standards have been updated. (5)

In the Ph. Eur. there is a section in the "Tablets" monography, which refers to the "Subdivision of Tablets". In those paragraphs, it is said that the competent authority must authorize the subdivision if the purpose of it is to obtain doses

accordingly to posology. That authorization must be based on an assessment of mass uniformity, which takes place in the developing phase. A total of thirty tablets is split by hand. From each whole tablet only one part is used to calculate the deviation, in comparison to the average mass. This value should be between 85% and 115% of the average mass. Not more than one tablet should position outside these limits, and no tablet can be outside the limits 75% to 125%. (11) This assessment should either occur during product development or for validation purposes. (12)

1.2.2 Stimuli article from the United States Pharmacopeial Convention

In this article, published in 2009, standards for the United States Pharmacopeia (USP) are proposed, regarding the subdivision of tablets. This proposal is based on research studies done by other entities and the "Tablets" monograph from the Ph. Eur.. It is also recognised, based on one of the referred studies, that three quality attributes can define the performance of score lines. These attributes are examined in the document. The first is "accuracy of subdivision", considered the most important out of the three. To establish this standard the proponents adopted the testing and limits of the Ph. Eur., although not adopting the same spectrum of application. This dissimilarity is based on the facts that in this document it is not supported that all scored tablets should be tested, but only those whose purpose of scoring is to adjust the dose. In addition, it is defended that the standards should not rely on posology schemes also because it is subjective and because that creates omission in case of off-label usage. The second attribute is the "loss of mass", and since no limit for this matter was yet established it is proposed a limit of $\leq$ 3% mean loss of mass upon subdivision. The third and last one is the "ease of breaking" or "ease of subdivision", which is described to be independent of the other two quality attributes. It was considered that the USP should adopt a standard for this matter, and to do so it should be done with "real world testing". However, it would not be workable for batch-to-batch testing. Alternatively, it is said that at least every batch should be assessed on these attributes, and that they should comply with the established standards. (5)

1.2.3 FDA approach to tablet scoring

On 2011, FDA published the draft of a document "Guidance For Industry – Tablet Scoring: Nomenclature, Labelling, and Data for Evaluation", that reflects

recommendations of the agency, not only so that new applications of scored tablets are more likely to be approved but also in the matter of labelling such products. These apply either to reference drugs and generic drugs since they should have consistent scoring. This has special relevancy if the aim of the score line is to adjust the dose. For instance, for the patient to be able to switch between brands without compromising the quantity of the active substance present in each halve, the generic should have a score line if the RLD has one. Also, it should not have a score mark if the RLD does not, because that would generate an imbalanced competition on the market. Furthermore, it mentions safety issues regarding the content of each halve if a tablet either was not tested for tablet subdivision or if it does not have a score line at all, especially because tablet subdivision has become a recurrent practice.

This guidance also introduces the concept of "functional scoring". The term is applied if the tablet complies with established criteria, therefore communicating that information to healthcare providers. For that reason, it is recommended that manufacturers update the prescribing information where it is mandatory to state that the product is scored to it having a "functional scoring". Not only is there a concern with the inclusion of a reference to scoring, but also it is mentioned that when tablets do not meet the established criteria there should be no referral of a score line or similar words, e.g. bisected, nor should this feature be present in the tablet.

Moreover, the guidance mentions cases when tablets should not have a score line, namely: the obtainment of under therapeutic range doses when a tablet is subdivided; drug exposure with risk for the person who is breaking it; and disruption of modified release systems. There is also a concern when halves of tablets are stored in containers, so stability in specific conditions should be tested. Finally, it is suggested that tablet halves should have to meet the same criteria as a whole tablet with the same strength.

Apart from Modified Release tablets for which additional criteria regarding dissolution is added, there are three assessments that should be done in solid oral dosage forms, namely in the split tablets: weight variation/content uniformity (as described in the USP <905>, "Uniformity of Dosage Units"; tablet splitability (at both ends of the proposed hardness range) regarding mass loss and friability; and dissolution assays. It is also suggested that these assessments are done not only during the Pharmaceutical Development but also with stability batches and scale-up. (1)

1.2.4 The United States Pharmacopeia approach

The USP <705> ("Quality Atributes of Tablets Labelled as Having a Functional Score") includes three tests to which split portions of functional scored tablets should comply to. However only the first test, "Splitting Tablets with Functional Scoring" assesses the accuracy of subdivision. This test has a quite different approach from the Ph. Eur. "Subdivision of tablets" testing, depicted by the following aspects. To begin with, both split fragments are analysed. Another reason why they differ is because the mass deviation is in comparison to the expected weight of each fragment (obtained dividing the weight of a whole tablet), instead of being in comparison to an average mass. Thirdly, this obtained deviation should be located between the limits of 75% and 125%, the acceptance criteria being that not more than two out of the thirty tablets fail to comply with the test.

Other relevant aspects are mentioned. First, that the subdivision is done using only hands, with no "mechanical assistance". It is also expressed a concern regarding storage conditions and period for the split tablets. And finally, regarding labelling, it is mentioned that the intended dose after subdivision should be stated in such documents. (13)

1.2.5 WHO Prequalification of Medicines Programme Guidelines

In the context of this programme, manufacturers can submit their Expression of Interest relatively to products for which subdivision of the tablet is required. Therefore, there are Guidelines regarding quality that include requirements for the acceptance of functionally scored tablets. For example, it is required that a dose uniformity testing for the split tablets (mass uniformity or content uniformity for special cases) is done - in both fragments of at least ten tablets - and that information about the method is provided, including detailed results - the mean, the deviation and individual values. The testing should also mimic the way the consumer would subdivide the tablet.

Concerning the labelling, namely the Summary of Product Characteristics (SmPC) and the package leaflet, the presence of a score and its intent should be referenced. (14) This is illustrated in another prequalification guidance document, the SmPC template, where three standard quotes are provided: "The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.", "The

tablet can be divided into equal halves." and "The tablet should not be divided." (15)

1.2.6 WHO Revision of Monograph on Tablets

In this document, critical steps of the manufacturing of tablets are described. In the case of scored tablets, which purpose is to subdivide into smaller doses, it is reiterated that during the development the effectiveness of break marks should be assessed. The described test is referred to mass uniformity and is based on the one described above by the Ph. Eur..

There is also a concern about labelling, implying that information about the storage of spilt tablets that are not intended to be taken right before the splitting, should be present in the label, as well as the conditions in which they should be stored. (16)

1.2.7 The European Medicines Agency approach to paediatrics and the elderly population

In two different moments, The European Medicines Agency (EMA) has expressed concern about two especially sensitive populations, regarding pharmaceutical development - the paediatric and the older population – as they sometimes have special modifications in oral intake of drugs. (17) (18)

First, in 2013 EMA published a Guideline regarding pharmaceutical development of medicines for paediatric use, which includes the case of scored tablets. It is denoted that the intended function of the score mark should be stated in the SmPC or the Patient Information Leaflet (PIL) and the suitability and ease of breaking should be demonstrated. It should also be stated if certain characteristics as being a modified release tablet nullify the splitting. In this specific population, it is sometimes needed to add either food or drinks with the medication, so it is considered important to provide information about compatibility with suggested vehicles. (17)

Then, in 2017 EMA published a reflection paper regarding pharmaceutical development of medicines for use in older population, also including the case of scored tablets. In the case of this population, some modifications should be made to either ease the intake or to lower the dose. Some examples of very relevant issues are brought up in this document. Regarding labelling, even though the scored tablets function is stated either in the SmPC or the PIL, sometimes the information on the physical leaflet is not yet up to date. Secondly, that when there are no alternatives,

off-label subdivision is sometimes recommended by healthcare professionals. Also, the discrepancy of the function of a score mark between brands is mentioned and finally the case where it is stated a tablet should not be subdivided despite it presenting a suggestive break mark. To resolve these issues, it is encouraged that all scored tablets regardless of its function break into equal parts and it is also suggested that companies started characterising the patient who would be comfortable breaking their tablets. Other suggested options are to the company to improve the breakability of tablets or to provide alternatives that would permit smaller doses. (18)

2 Objective

The aim of this dissertation was to determine if medicines marketed in Portugal were in conformity with the regulatory requirements regarding tablets subdivision. To do so a study with volunteers was performed. The objectives of this study were: to evaluate if mass loss during tablet subdivision is significant; and to quantify the ease of subdivision of tablets for the patient.

3 Materials and Methods

One of the aims of this research project was to assess the regulatory compliance of the subdivision of tablets bearing a break or score line. This assessment was performed by analyzing the result of breaking or splitting tablets, performed by volunteers, of a sample of medicines marketed in Portugal.

For that purpose, it was necessary to evaluate if mass loss during the splitting process was significant and in what kind of extension was this act a struggle for the patients. Certain steps took place prior to the referred study, described below.

3.1.1 Research

The starting point of the present work was to identify medicines marketed in Portugal bearing score lines. Since this research aimed to identify potentially problematic medicines regarding its correct breakability for the elderly patients, the chosen tablets contained drugs commonly used to treat chronic diseases. The database used was Infomed (19), from INFARMED. The Summary of Product Characteristics from each of the marketed chosen drugs dosage was consulted. The purpose was to find out which of the tablets had a score line and if so, what its purpose was. Even though some did not have that information, in the majority of the cases it was described that the score line had one of the three aims: to divide the tablet in two halves; to divide the tablet in equal dosages or to divide the tablet in order to ease the swallowing of it (and not to divide it into equal dosages).

Throughout the development of the present work, several articles were analysed using mostly the PubMed database, the Google Scholar web search engine and keywords, such as “tablet subdivision”, “tablet splitting”, “breakability of tablets”, “scored tablets”, “splitability of tablets”, “crumbling” and “regulatory requirements”. The selected articles were published between 2002 and 2018.

3.1.2 Codification of the tablets

The tablets used in the following assessments and experiment were kindly provided by a pharmaceutical company. They were selected, considering the presence of a score line and the number of units made available to perform the necessary pharmacotechnic tests and further assessment of the subdivision by the volunteers. They were then coded.

The codification was based on characteristics of the tablets, as shown in **Table 1**. The first digit corresponds to the shape of the tablet, "0" meaning oblong and "1" meaning round; the second digit reflects the aim of the score, "0" being to ease the swallowing of the tablet, "1" to divide it in equal dosages and "2" if the purpose of the score is not mentioned or if it is not clear; the third digit reflects the number of scores in one side of the tablet (e.g. 1, 2, 3, …) and the fourth digit is either "1" or "2" if the tablet is scored in only one side or both sides, respectively. The last two digits correspond to the identification number (from 01 to 21). Number "06" was cut out as there were not enough tablets to perform the assessment.

3.1.3 Characterisation of the tablets

The third phase took place at the laboratory in the Faculty of Pharmacy, University of Lisbon. It consisted in performing some physical and pharmacotechnic tests in order to characterize the tablets as well to assess its compliance with the regulatory requirements. As such, the tablet resistance to crushing (also designated as tablet hardness), was measured by using an ERWEKA® TBH 20 Tablet Hardness Tester (Erweka, Germany).

Then, the uniformity of mass test (Ph. Eur. 2.9.5) was performed. The assessment of the tablets splitability was performed upon weighing the whole tablets as well as the respective halves after splitting by using a AG204 Delta Range® scale (Mettler Toledo GmbH, Germany), coupled to a LC-P45 printer (Mettler Toledo GmbH, Germany). In addition, the tablets dimensions (diameters, thickness and the depth of the score line) were measured by using a Fischer Darex® sliding caliper and recorded. In the case of oblong tablets, the larger and smaller diameters) were recorded.

3.1.4 Preparation of the sets given to the volunteers

The succeeding step was to prepare the sets of tablets given to the volunteers to break. From the total of the twenty tablets only fifteen were used in the study, since some tablets presented such similarities that it would be redundant to use them as different observations. In addition, it was considered preferable to have a smaller number of different drug products but a larger number of observations per product than the other way round.

In order to minimize the inter-subject variability due to the intrinsically subjective perception of the difficulty in breaking the tablets, each set of tablets to be split by subjects included tablets from a "hard to break" and "easy to break" products. Tablets from these two "standard" products were broken, by the subjects, before the "test" products and would hopefully work as perception references to the ease of breakability.

The tablets chosen for each of the subjects was predetermined, prearranged and packed into individual plastic bags (**Figure 2**). as sets. In each of these given sets, tablets from four different drug products were provided, in a total of ten. A prediction model (9) helped to select these tablets, since it provided a prediction of which would be easier or more difficult for the subjects to break. Such prediction was important to classify the drug products according to the difficulty of breaking tablets and to establish standards.

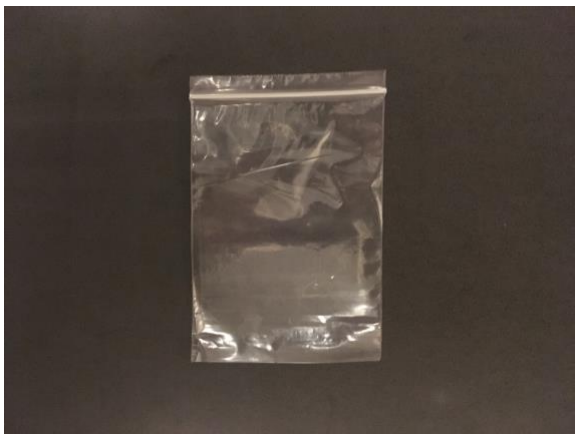

Figure 2. Plastic bags used to pack the sets of tablet

Table 1. Codification of the tablets

Codification of the tablets					
Code	**Shape of the tablet**	**Aim of the score**	**Number of scores (one side)**	**Number of scored sides**	**Identification Number**
121101	Round (1)	2	1	1	01
101102	Round (1)	0	1	1	02
001203	Oblong (0)	0	1	2	03
121104	Round (1)	2	1	1	04
021105	Oblong (0)	2	1	1	05
111207	Round (1)	1	1	2	07
111208	Round (1)	1	1	2	08
011109	Oblong (0)	1	1	1	09
021010	Oblong (0)	2	1	0	10
021111	Oblong (0)	2	1	1	11
021112	Oblong (0)	2	1	1	12
021113	Oblong (0)	2	1	1	13
011214	Oblong (0)	1	1	2	14
011215	Oblong (0)	1	1	2	15
011116	Oblong (0)	1	1	1	16
021217	Oblong (0)	2	1	2	17
021118	Oblong (0)	2	1	1	18
121119	Round (1)	2	1	1	19
021220	Oblong (0)	2	1	2	20
121121	Round (1)	2	1	1	21

According to this model, in the case of round tablets, the physical parameters that shown to have a larger contribution to the ease of subdivision were: resistance to crushing, the diameter, the presence of a score mark that was either one-sided (“0”) or two-sided (“1”), the thickness and the shape, meaning if the tablet was either a biconvex tablet (“0”) or a flat tablet (“1”). In the case of oblong tablets, there were also parameters considered to be crucial for the ease of subdivision: the diameter, the depth of the score line, the diameter/width ratio and the resistance to crushing. However, the prediction model applied to oblong tablets, instead of having a formula as round tablets, each parameter had a cut off limit. In order to the ease of subdivision to be at least eighty percent, all parameters had to meet these acceptance criteria. Unfortunately, when applied to the tablets for this study, none of the tablets met all the criteria, therefore the prediction model was unable to provide enough information for the selection of standards from all the products available. In addition to the referred model, three non-trained volunteers classified the tablets regarding their perception of the ease of breakability.

Subsequently, in each set given to the volunteer, two out of the four different tablets in each set were considered standards. One of the standards belonged to a group of three tablets - considered very difficult or almost impossible to break – them being 121104, 111208 and 011116. A second standard belonged to another group of tablets - considered easily breakable – them being 121101, 011203 and 021105. Each of the standards were repeated twice, making a total of four tablets (out of ten in total). The other two tablets from each set were chosen from a group of nine tablets, namely 101102, 111207, 011109, 021010, 021111, 021112, 021113, 011214, 011215, 021217, 021118, 121119, 021220 and 121121. These two different tablets were repeated thrice, making a total of six tablets (out of ten in total).

3.1.5 Study with volunteers

The third phase consisted of the assessment of the ease of breakability by subjects (volunteers) as well as the weighing of the resulting tablets fractions. It was performed at a community pharmacy, in Castelo Branco, Portugal (Farmácia Ferrer, Lda.), in which volunteers meeting the inclusion criteria - elderly with a physical appearance corresponding to a person of not less than fifty-years old, with no apparent

handicap that would limit the ability to split the tablets - were invited by the pharmacists or pharmacy technicians to participate in the study, and conducted to a separate room. In this room, a brief description of the aim of this project was given to the volunteers and they were asked to break, by hand, ten tablets as they would in their homes (without mechanical assistance (13)). No suggestion of breaking methods was provided, since it could bias the outcomes of the study. The volunteers were also told that they would not, in any circumstances swallow the tablets after their splitting (as recommended in (5) – "Care should be taken that the panelist does not swallow the tablet before or after breaking").

The tablets were given to subjects in a predefined non-random sequence, as exemplified in **Table 2**.

Table 2. Scheme of the sequence of subdivision for each set

Number of tablet	Type
1	"Easy" Standard 1
2	"Hard" Standard 1
3	Test 1
4	Test 2
5	"Hard" Standard 1
6	Test 2
7	Test 1
8	"Easy" Standard 1
9	Test 1
10	Test 2

To meet the recommendation of using 30 tablets to assess the tablet subdivision (5)(11), 47 subjects were enrolled in the study.

The volunteers were also asked to quantify their effort while breaking each of the tablets. To ease the level of breakability evaluation by the volunteer, an illustration was shown at the beginning of the experiment **Figure 3**.

Figure 3. Illustration created to ease the evaluation by the patient

Each of the halves of the broken tablets or the whole tablet in case of failure to break were placed into numbered compartments of common weekly tablet organizers (**Figure 4**). These fractions, resulting from the tablets broken by the volunteers, were weighted by using a Sartorius ED153-PCE scale (Sartorius, Germany) to evaluate the fractions weight similarity as well as the loss of mass due to crumbles during the breaking of tablets.

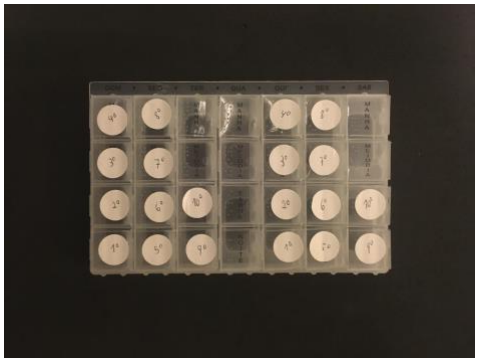

Figure 4. Weekly tablet organizers used to store tablets (whole and fragments)

3.1.6 Data analysis

Three different outcomes were recorded for each tablet break:

a) the success in breaking the tablet (was the volunteer able/unable to break the tablet?)
b) the level of difficulty, in breaking the tablet, reported by the volunteer
c) the mass of all the fractions resulting from breaking the tablet

The results were arranged and compiled into tables, for data analysis.

4 Results

4.1 Characterisation of the tablets

Two assessments were made previously to the study. The first was the measurement of tablet resistance to crushing (tablet hardness). Ten tablets of each of the twenty different tablets were measured. The average value as well as the range of tablet resistance to crushing of each tablet are shown in **Table 3**.

Table 3. Tablet resistance to crushing (expressed in Newtons)

Code	Minimum value	Maximum value	Average value
121101	53	66	60
101102	57	66	61
001203	279	369	339
121104	74	84	79
021105	50	80	67
111207	127	191	166
111208	199	245	214
011109	142	181	166
021010	78	118	105
021111	107	237	193
021112	176	218	192
021113	143	185	169
011214	96	139	113
011215	176	251	223
011116	107	126	115
021217	200	299	237
021118	84	99	90
121119	54	64	59
021220	164	238	202
121121	61	74	67

Combining the resistance to crushing to measured parameters - as diameter and thickness – and visual parameters – as score mark (one-sided or two-sided) and shape (biconvex or flat) – it was possible to apply the prediction model to round tablets. (**Table 4**)

Table 4. Prediction model applied to round tablets

Round Tablets						
Code	**Resistance to crushing (N)**	**Diameter (mm)**	**Score mark**	**Thickness (mm)**	**Shape**	**Result (%)**
121101	60	12,63	0	3,27	1	**99**
101102	61	8,04	0	3,44	1	**51**
121104	79	8,05	0	4,43	0	**32**
111207	166	7,94	1	2,46	0	**82**
111208	214	9,92	1	3,36	0	**62**
121119	59	10,08	0	3,48	1	**90**
121121	67	10,64	0	4,26	0	**93**

*Legend: Score mark - **0** if one-sided, **1** if two-sided; Shape - **0** if biconvex, **1** if flat*

Combining the resistance to crushing to measured parameters - as diameter, width and depth of score line – it was possible to apply the prediction model to oblong tablets. (**Table 5**)

Then, the whole tablets and their respective halves after splitting were weighted. Twenty tablets of each of the twenty different tablets were measured. The average whole tablet weight as well as the minimum and maximum values are shown in **Table 6** , and the tablet halves weight is shown in **Table 7** (Halves A) and **Table 8** (Halves B). It is also shown, in each of these tables, the deviation of the minimum and maximum values. Summarizing aspects of these tablets are shown in **Table 9**, namely the mass loss - obtained from the sum of the halves weight in comparison with the average whole tablet weight, and the deviation of the average weight of halves A in comparison to the average weight of halves B.

Table 5 . Prediction model applied to oblong tablets

Oblong tablets						
Code	Diameter (mm)	Diameter//Width ratio	Depth of score line	Resistance to crushing (N)	**Result**	**Criteria Met**
	Acceptance criteria					
	≥ 10 mm	≥ 2.0	≥ 0.5 mm	≤ 100 N		
001203	13,11	2,53	0,37	339	≤ 0.800	**2/4**
021105	9,05	2,25	0,79	68	≤ 0.800	**3/4**
011109	12,17	1,98	0,83	166	≤ 0.800	**2/4**
021010	11,58	1,63	0,15	105	≤ 0.800	**1/4**
021111	10,20	1,97	0,27	193	≤ 0.800	**1/4**
021112	10,20	1,97	0,42	192	≤ 0.800	**1/4**
021113	10,26	1,98	0,38	169	≤ 0.800	**1/4**
011214	10,08	1,96	0,25	113	≤ 0.800	**1/4**
011215	11,23	1,96	0,11	223	≤ 0.800	**1/4**
011116	10,10	1,99	0,17	115	≤ 0.800	**1/4**
021217	11,27	1,96	0,09	237	≤ 0.800	**1/4**
021118	8,07	1,44	0,05	90	≤ 0.800	**1/4**
021220	11,29	4,30	0,10	202	≤ 0.800	**2/4**

Table 6. Whole tablet weight

Code	Whole tablet weight			Deviation	
	AVG	MIN	MAX	MIN (%)	MAX(%)
121101	483,76	474,4	491,9	-1,90	1,70
101102	181,12	178,4	184,8	-1,50	2,00
001203	272,22	265,2	278,3	-2,60	2,20
121104	181,4	176,9	186,0	-2,50	2,50
021105	91,32	89,8	92,2	-1,70	1,00
111207	182,47	177,4	186,1	-2,80	2,00
111208	365,77	360,6	369,4	-1,40	1,00
011109	269,08	263,7	273,3	-2,00	1,60
021010	243,86	239,9	246,2	-1,60	1,00
021111	181,48	170,1	188,1	-6,30	3,60
021112	184,39	181,5	186,5	-1,60	1,10
021113	1814,2	177,8	183,8	-2,00	1,30
011214	171,02	167,6	174,9	-2,00	2,30
011215	170,57	166,7	173,4	-2,30	1,70
011116	183,58	181,1	187,4	-1,40	2,10
021217	170,27	164,3	175,2	-3,51	2,90
021118	121,1	119,9	123,2	-0,99	1,73
121119	324,16	322,1	326,5	-0,64	0,72
021220	170,24	163,6	176,1	-3,90	3,40
121121	402,17	394,1	408,7	-2,01	1,62

Legend: AVG - Average value; MIN – Minimum value; MAX – Maximum Value. Mass measured in milligrams

Table 7. Tablet halves weight (Halves A)

Code	Weight of Halve A			Deviation	
	AVG	MIN	MAX	MIN (%)	MAX(%)
121101	235,06	259,6	208,1	10,40	-11,50
101102	90,73	85,8	94,6	-5,40	4,30
001203	134,12	122,7	144,8	-8,50	8,00
121104	89,78	70,9	108,3	-21,00	20,60
021105	45,24	40,8	48,7	-9,80	7,60
111207	92,36	88,6	96,7	-4,10	4,70
111208	184,78	174,7	191,1	-5,50	3,40
011109	140,61	128,0	156,3	-9,00	11,20
021010	123,15	115,4	134,8	-6,30	9,50
021111	87,56	79,8	99,7	-8,90	13,90
021112	86,64	79,6	101,3	-8,10	16,90
021113	83,89	72,4	97,5	-13,70	16,20
011214	82,96	75,9	88,0	-8,50	6,10
011215	84,91	77,6	90,5	-8,60	6,60
011116	92,8	87,7	98,3	-5,50	5,90
021217	83,28	47,1	11,19	-43,44	34,37
021118	61,03	57,7	63,4	-5,46	3,88
121119	145,74	109,4	168,8	-24,93	15,82
021220	904,7	80,1	115,7	-91,10	-87,20
121121	199,99	184,4	248,6	-7,80	24,31

Legend: AVG - Average value; MIN – Minimum value; MAX – Maximum Value.
Mass measured in milligrams

Table 8. Tablet halves weight (Halves B)

Code	Weight of Halve B			Deviation	
	AVG	MIN	MAX	MIN (%)	MAX(%)
121101	247,96	274,9	223,4	10,90	-9,90
101102	90,24	85,2	94,7	-5,60	4,90
001203	137,95	126,1	148,9	-8,60	7,90
121104	91,49	73,9	112,4	-19,20	22,90
021105	46,06	43,0	50,0	-6,60	8,60
111207	90,14	83,7	94,8	-7,10	5,20
111208	180,88	175,3	190,7	-3,10	5,40
011109	128,44	113,3	144,1	-11,80	12,20
021010	122,16	110,3	129,6	-9,70	6,10
021111	93,66	78,7	102,6	-16,00	9,50
021112	97,67	84,8	104,6	-13,20	7,10
021113	97,02	83,9	108,0	-13,50	11,30
011214	87,17	82,2	91,5	-5,70	5,00
011215	85,64	78,7	89,7	-8,10	4,70
011116	90,36	83,4	95,1	-7,70	5,20
021217	87,05	57,1	124,4	-34,41	42,91
021118	60,62	57,3	64,4	-5,48	6,24
121119	178,15	153,7	212,5	-13,72	19,28
021220	79,86	53,3	86,9	-33,30	-8,80
121121	202,19	153,0	214,7	-24,33	6,18

Legend: AVG - Average value; MIN – Minimum value; MAX – Maximum Value.
Mass measured in milligrams

Table 9. Mass loss and mass deviation

Code	AVG whole tablet weight	AVG Weight of Halve A + AVG Weight of Halve B	Mass loss (%)	Deviation Halve A/ Halve B (%)
121101	483,76	483,02	-0,15	-5,20
101102	181,12	180,97	-0,08	0,50
001203	272,22	272,07	-0,06	-2,80
121104	181,4	181,27	-0,07	-1,90
021105	91,32	91,3	-0,02	-1,80
111207	182,47	182,5	0,02	2,50
111208	365,77	365,66	-0,03	2,20
011109	269,08	269,05	-0,01	9,50
021010	243,86	245,31	0,59	0,80
021111	181,48	181,22	-0,14	-6,50
021112	184,39	184,31	-0,04	-11,30
021113	181,42	180,91	-0,28	-13,50
011214	171,02	170,13	-0,52	-4,80
011215	170,57	170,55	-0,01	-0,90
011116	183,58	183,16	-0,23	2,70
021217	170,27	170,33	0,04	-4,33
021118	121,1	121,65	0,45	0,68
121119	324,16	323,89	-0,08	-18,19
021220	170,24	170,33	0,05	13,30
121121	402,17	402,18	0,00	-1,09

Legend: AVG - Average value. Mass measured in milligrams

4.2 Breakability assessment study

This study had a total of 47 participants, each of them breaking a total of ten tablets. Therefore, there was a total of 470 observations.

4.2.1 Ability to break the tablets

Out of the 470 observations, a total of 42 tablets were not broken. This means that volunteers were not able to break 8,94% of all the tablets that volunteers tried to break.

Out of the 15 tablets in the study, 5 of them belonged to this group of tablets that were not broken by the volunteers. Tablets with the codes 121104, 111208 and 011116, belonged to the "Hard" Standards, which means that volunteers were not able to break 7,87% of the "Hard" Standards. The other tablets – 121121 and 101102 belonged to the test tablets group. Results are shown in **Table 10**.

Table 10. Tablets that volunteers were not able to break

Code	Occurences	Occurences of "Hard" Standards Tablets
101102	3	-
121104	18	18
111208	16	16
011116	3	3
121121	2	-
Total	**42**	**37**

4.2.2 Mass loss

After the volunteers broke the tablets that were given to them, both of the halves of each tablet were weighted. Both weights of each tablet were summed, obtaining the mass that was not lost due to powdering or crumbling, shown in **Table 11**.

The deviation of this value in comparison to the average mass - previously calculated in **Table 6** - is shown in **Table 12**. A limit of 5% of mass loss was adopted.

Table 11. Weights of each halves and their sum

Code	Halves A weight			Halves B weight			Halves A+B weight		
	AVG	MIN	MAX	AVG	MIN	MAX	AVG	MIN	MAX
121101	244,5	157	283	237,2	208	318	481,7	451	495
101102	89,3	41	140	83,8	17	97	173,1	124	186
001203	138,8	123	167	132,4	101	151	271,1	263	281
121104	95,1	78	112	83,2	55	107	178,3	162	186
021105	46,7	37	60	44,7	31	52	91,4	88	95
111208	182,4	174	193	180,2	146	191	362,6	339	370
011109	136,5	123	148	134,6	124	151	271,1	260	278
021010	126,2	95	144	120,6	87	140	246,8	182	256
021111	92,5	82	104	89,6	78	103	182,0	168	188
011214	84,2	77	91	85,9	76	101	170,1	158	186
011116	91,7	83	104	91,4	80	101	183,2	178	188
021118	59,7	44	71	64,2	51	82	123,9	117	130
121119	162,6	125	195	159,4	84	197	322,0	228	333
021220	86,2	67	94	86,2	79	103	172,4	168	180
121121	200,5	176	241	200,9	137	227	401,5	378	408

Legend: AVG - Average value; MIN – Minimum value; MAX – Maximum Value. Mass measured in milligrams

Table 12. Mass loss

Code	Halves A weight (mg)			Halves B weight (mg)			Halves A+B weight (mg)		
	AVG	MIN	MAX	AVG	MIN	MAX	AVG	MIN	MAX
121101	50,5	32,5	58,5	49,0	43,0	65,7	99,6	93,2	102,3
101102	49,3	22,6	77,3	46,3	9,4	53,6	95,6	68,5	102,7
001203	51,0	45,2	61,3	48,6	37,1	55,5	99,6	96,6	103,2
121104	52,4	43,0	61,7	45,9	30,3	59,0	98,3	89,3	102,5
021105	51,1	40,5	65,7	48,9	33,9	56,9	100,1	96,4	104,0
111208	49,9	47,6	52,8	49,3	39,9	52,2	99,1	92,7	101,2
011109	50,7	45,7	55,0	50,0	46,1	56,1	100,8	96,6	103,3
021010	51,7	39,0	59,1	49,5	35,7	57,4	101,2	74,6	105,0
021111	50,9	45,2	57,3	49,4	43,0	56,8	100,3	92,6	103,6
011214	49,3	45,0	53,2	50,2	44,4	59,1	99,5	92,4	108,8
011116	50,0	45,2	56,7	49,8	43,6	55,0	99,8	97,0	102,4
021118	49,3	36,3	58,6	53,0	42,1	67,7	102,3	96,6	107,3
121119	50,2	38,6	60,2	49,2	25,9	60,8	99,3	70,3	102,7
021220	50,6	39,4	55,2	50,6	46,4	60,5	101,3	98,7	105,7
121121	49,9	43,8	59,9	50,0	34,1	56,4	99,8	94,0	101,4

Legend: AVG - Average value; MIN – Minimum value; MAX – Maximum Value.
Mass measured in milligrams

4.2.3 Non compliances

Out of the 470 observations, a total of 6 tablets split in more than 2 fragments, which represents a total of 1,28% of all the tablets that volunteers tried to break. Results are shown in **Table 13**.

Table 13. Number of non compliances

Code	Occurences
121101	1
101102	3
121104	1
121119	1
Total	**6**

4.2.4 Ease of subdivision

It was asked that the volunteers quantify their effort whilst breaking each of the tablets that were given to them. In case of the tablets that the volunteers were able to break the tablet, the score could be "1" if it was very hard for the volunteers to break the tablet; "2" if it was relatively difficult; "3" if it was relatively easy; and "4" if it was very easy to break the tablet. The results are shown in **Table 14** . An average of the answers given by volunteers for each tablet is shown in **Table 15**.

Table 14. Answers of the volunteers regarding ease of subdivision

Score	Number of Answers	Percentage (%)
"1"	25	5,32
"2"	32	6,81
"3"	135	28,72
"4"	236	50,21
Not able to break the tablet	42	8,94

Table 15. Ease of subdivision score

Tablet Group	Code	Ease of subdivision score average
"Easy" Standards	**121101**	3,63
	001203	3,69
	021105	3,53
"Hard" Standards	**121104**	1,71
	111208	1,43
	011116	2,59
Test Tablets	**101102**	2,96
	011109	3,77
	021010	3,67
	021111	3,73
	011214	3,67
	021118	2,83
	121119	3,52
	021220	3,76
	121121	3,77

4.3 Crossover data

4.3.1 Broken tablets – Model prediction and experimental observations

In this section, a comparison between the prediction of the model (regarding how many volunteers would be able to break the tablets) and what actually occurred in the assessment of breakability study (percentage of broken tablets and an average value of the score volunteers attributed to the ease of breakability) is made. Results in **Table 16** apply to round tablets and results in **Table 17** apply to oblong tablets.

Table 16. Volunteers ability to break round tablets and their perception

Code	Model Prediction (%)	Breakability assessment study	
		Percentage of broken tablets (%)	Ease of subdivision score (AVG)
121101	99	100,00	3,63
101102	51	93,33	2,96
121104	32	43,75	1,71
111208	62	46,67	1,43
121119	90	100,00	3,52
121121	93	93,94	3,77

Legend: AVG - Average value.

Table 17. Volunteers ability to break oblong tablets and their perception

	Model prediction		Breakability assessment study	
	Result	Criteria Met	Percentage of broken tablets (%)	**Ease of subdivision score (AVG)**
001203	≤ 0.800	2/4	100,00	3,69
021105	≤ 0.800	3/4	100,00	3,53
011109	≤ 0.800	2/4	100,00	3,77
021010	≤ 0.800	1/4	100,00	3,67
021111	≤ 0.800	1/4	100,00	3,73
011214	≤ 0.800	1/4	100,00	3,67
011116	≤ 0.800	1/4	90,63	2,59
021118	≤ 0.800	1/4	100,00	2,83
021220	≤ 0.800	2/4	100,00	3,76

Legend: AVG - Average value.

4.3.2 Ease of subdivision *versus* Resistance to Crushing

In **Table 18** a comparison between the average value of the score volunteers attributed to the ease of breakability of tablets and the resistance to crushing (average value) is done. It is possible to compare these values according to the group of tablets – "hard" standards, "easy" standards and the test tablets group.

Table 18. Ease of subdivision *versus* resistance to crushing

Tablet Group	Code	Shape	Ease of subdivision score (AVG)	Resistance to crushing (N)
"Easy" Standards	**121101**	Round	3,63	60
	001203	Oblong	3,69	339
	021105	Oblong	3,53	67
"Hard" Standards	**121104**	Round	1,71	79
	111208	Round	1,43	214
	011116	Oblong	2,59	115
Test Tablets	**101102**	Round	2,96	61
	011109	Oblong	3,77	166
	021010	Oblong	3,67	106
	021111	Oblong	3,73	193
	011214	Oblong	3,67	113
	021118	Oblong	2,83	90
	121119	Round	3,52	59
	021220	Oblong	3,76	202
	121121	Round	3,77	67

Legend: AVG - Average value.

4.3.3 Mass deviation – Assessments of Mass uniformity *versus* breakability study

In **Table 19** it is done a comparison between the results previous to the breakability assessment study, done in the faculty laboratory and the results from the study in the community pharmacy. These results represent the mass deviation of the whole tablets and the sum of their halves to the same value (average mass of each tablet done previously in the mass uniformity test).

Table 19. Mass deviations

	Assessment of mass uniformity (faculty laboratory)			Breakability assessment study (pharmacy laboratory)		
	Halves A AD. (%)	Halves B A.D. (%)	Halves A+ B A.D. (%)	Halves A A.D. (%)	Halves B A.D. (%)	Halves A+ B A.D. (%)
121101	48,59	51,26	99,85	50,5	49,0	99,6
101102	50,09	49,82	99,92	49,3	46,3	95,6
001203	49,27	50,68	99,94	51,0	48,6	99,6
121104	49,49	50,44	99,93	52,4	45,9	98,3
021105	49,54	50,44	99,98	51,1	48,9	100,1
111208	50,52	49,45	99,97	49,9	49,3	99,1
011109	52,26	47,73	99,99	50,7	50,0	100,8
021010	50,50	50,09	100,59	51,7	49,5	101,2
021111	48,25	51,61	99,86	50,9	49,4	100,3
011214	48,51	50,97	99,48	49,3	50,2	99,5
011116	50,55	49,22	99,77	50,0	49,8	99,8
021118	50,40	50,06	100,45	49,3	53,0	102,3
121119	44,96	54,96	99,92	50,2	49,2	99,3
021220	53,14	46,91	100,05	50,6	50,6	101,3
121121	49,73	50,27	100,00	49,9	50,0	99,8

Legend: A.D. - Average value Deviation. Mass measured in milligrams

5 Discussion

Out of the 470 observations of the breakability assessment study, some tablets were not broken (**Table 10**) or were broken but in more than two fragments (**Table 13**).

Overall, the volunteers were not able to break a total of 8,94% of the tablets (as shown in **Figure 5**), which is a quite significant amount of scored tablets that part of a the population probably wo not be able to break. From these tablets, 7,87% were from the group of "hard" standards (as shown in **Figure 6**).

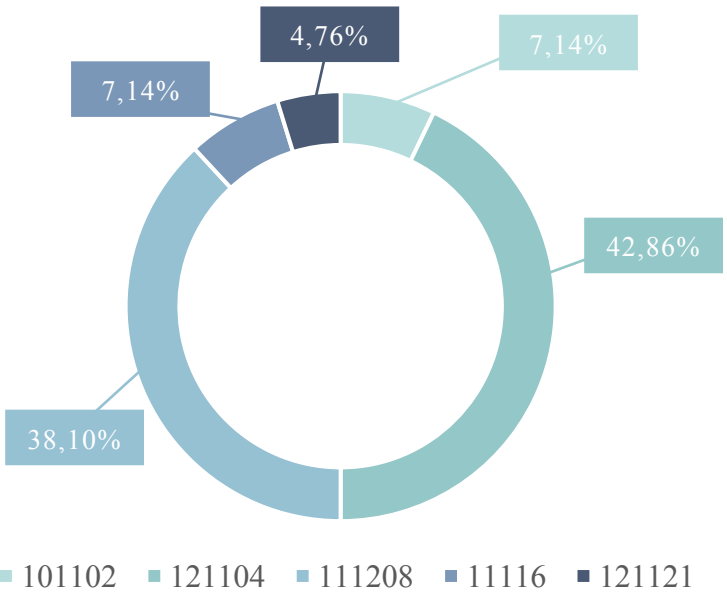

Figure 5. Tablets that volunteers were not able to break

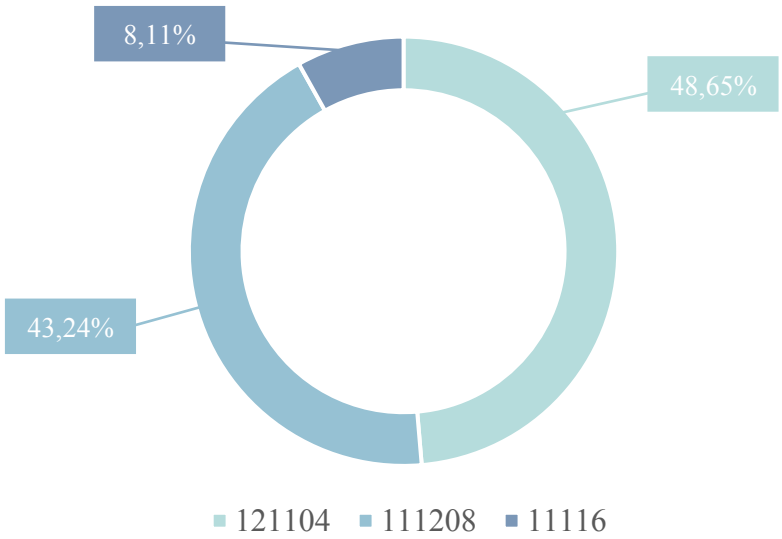

Figure 6. "Hard" standard tablets that volunteers were not able to break

These three "standards" are also the three tablets with the three lower scores in terms of perception of ease of breakability from the volunteers (shown **in Table 15**). Also, from these, 121104 and 111208 had a higher expression of non-broken tablets than 011116, and 011116 had a significant higher score regarding its ease of breakability, which supports the fact that these were the tablets with such findings.

Regarding the other two tablets, 121121 and 101102 (test tablets), two distinct situations occurred:

a) Two different volunteers (A and B, as shown in **Figure 7**) were not able to break tablet 101102. In both of them it corresponded to the second 101102 tablet out of three that were in their respective sets. Both were not able to break their respective "hard" standards tablets included in his sets (One had tablet 111208 and the other had tablet 011116). This probably means that the reason for both volunteers not to be able to break tablet 101102 is a patient-related cause. Nevertheless this situation has to be foreseen and therefore preventive measures should be taken by manufacturers.

b) A third volunteer (C, as shown in **Figure 7**) was not able to break two out of three tablets 121121 (second and third in the set); this volunteer also was not able to break the first out of three 101102 tablets, and the other two broke in more than two fragments. This same volunteer was also not

able to break the respective “hard” standard tablets included in the given set (tablet 121104), so this situation can also classify as a patient-related cause.

Figure 7. Examples of volunteers outcomes

Legend: ✔ - tablet was broken by the volunteer; × - tablet was not broken by the volunteer; **F** *– tablet was fragmented in more than the two expected fragments.*

From the tablets that broke into more than two fragments (**Table 13**), the most occurrences were with tablet 101102, two of which were the case of the above referred volunteer (C, as shown in **Figure 7**). This volunteer was not able to break a total of five tablets (four prior to the two non compliances and one afterwards). The other occurrence of this non compliance with tablet 101102 was by a volunteer that could not break both two tablets 111208 given in his set. Since 111208 is a “hard” standard, a possible cause could be that the effort that the volunteer had to apply to “hard” standards tablets was of such intensity that when applied the same amount of effort into tablet 101102 - which has one of the lowest values of resistance to crushing (61 N) - it broke in more than two fragments, which should not happen in any circumstances. This supposition might apply as well to the situation above.

The other three tablets that broke in more than two fragments were 121101, 121104 and 121119, each of them by different volunteers, that were all able to break the “hard” standards tablets given in their sets.

In conclusion, a total of six tablets out of the 470 observations broke in more than two fragments, representing 1,28% (proportion of the tablets shown in). This value in addition to the tablets that were not broken, sums up to a significant total of 10,22% that did not break into the desired and expected halves.

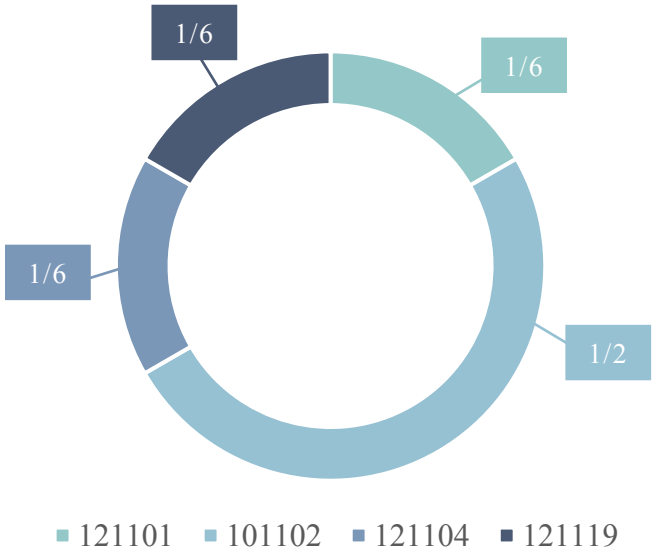

Figure 8. Proportion of tablets that broke in more than two fragments

In **Table 14** the scores that volunteers attributed according to their perception of effort while breaking each tablet are grouped. This data (graphic representation shown in **Figure 9**) allows to conclude that:

a) around a third (28,72%) answered that the tablets were relatively easy and that around half (50,21%) of the volunteers answered that that the tablets were very easy to break. These findings sugest that the the test group tablets (60%) and "easy" standards (20%), should be distributed in these two categories (relatively or very easy to break)

b) and that around a fifth (21,07%) of the volunteers answered that either the tablets were difficult (6,81%), very difficult (5,32%) or that they were not able to break the tablets (8,94%), which is coherent to the percentage of "hard" standards.

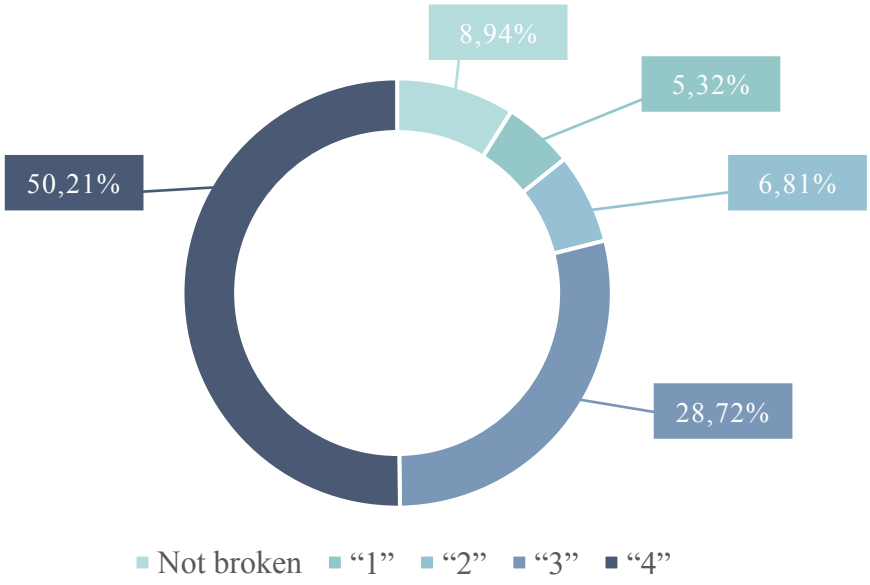

Figure 9. Score attributed by the volunteers

Data in **Table 15**Ease of subdivision score support these findings since the "hard" standard have the three lowest scores regarding the ease of subdivision, and that "easy" standards have similar scores to the highest scored "test" groups. Additionally, the average score of the ease of subdivision of tablets 121119, 101102 and 021118 is the lowest out of the test and "easy" standards, suggesting that these are the tablets that were considered somewhat difficult to break. Therefore, the group that represents a fifth of the results might be formed not only by the tablets that volunteers were not able to break but also by the three "hard" standards and these three tablets (121119, 101102 and 021118) – the six with the lowest attributed score regarding the ease of subdivision.

The ability to forecast of the prediction model is compared to what occurred in the breakability assessment study. In **Table 16** the results are in respect to round tablets. The model predicted that tablets 121101, 121119 and 121121 would be the tablets that a larger number of subjects would be able to break. This prediction corresponds to the three round tablets with higher percentage of broken tablets in the study and it is also coherent to the finding regarding the score attributed (by the volunteers) to the ease of subdivision of such tablets. Also, tablet 121104, which had the lowest predicted percentage of subjects that could break the tablets is also the tablet with the lowest percentage of broken tablets in the study. In **Table 17** (regarding oblong tablets), the scenario is different since the model had an "all-or-nothing" criteria. Nevertheless, the criteria that the tablets fraction of criteria that the

tablets met can be used as a comparative parameter. The tablet that fewer volunteers were able to break was tablet 011116, which only met one of the criteria and has the smaller score attributed (by the volunteers) regarding ease of subdivision.

In **Table 18** the average breakability value (given by the volunteers) is allied to the average resistance to crushing of the tablets. Also, tablets are tagged regarding its shape (if they are round or oblong tablets).

The three tablets that present lowest breakability scores -1,71; 1,43; and 2,59 - are also the tablets considered the "hard" standards - 121104, 111208 and 011116, respectively. These findings are coherent with two tablets regarding their resistance to crushing, since 111208 has the second highest value (214 N) and 011116 the sixth highest value (115 N). Tablet 121104 has a lower resistance value (79 N) so the physical hardness of this tablet is probably not the major factor for its difficulty in subdivision. For instance, it could be due to its very shallow depth of the score line and the fact that it is one sided.

Another finding regarding these results is that five (121101, 101102, 121104, 121119, 121121) out of the six round tablets have the five lowest resistance to crushing values (60 N, 61 N, 79 N, 59 N and 67 N, respectively). Despite this fact, only number 121121 has a higher score, the highest out of all the tablets (and the same as 011109). Therefore we can not imply that the shape of the tablet has an effect on the ease of breakability, even though the three tablets with the higher score are round (121121, 011109 and 021220).

In the mass uniformity assessment phase, occurred in the laboratory of the Faculty of Pharmacy, University of Lisbon, twenty tablets of each of the available products were tested, both the whole tablets and their respective halves. Results are shown in **Table 6** to **Table 9**.

Regarding halves A (**Table 7**), tablets 121104, 021112, 021113 and 021220 showed important deviations, of more than 15% according to the Ph. Eur. 9.2.5 (regarding the minimum and maximum values) from the average mass. From these tablets 121104 and 021220 were selected to do the study with the volunteers.

Regarding halves B (**Table 8**), tablets 021111 and 021220 also showed the same important deviations, from the average mass. Both these tablets were selected to do the study with the volunteers. These findings should predict what would occur in the breakability assessment study.

From these tablets, tablet 021220 has one of the largest deviation between halve A and halve B, (alongside with 121119) which should also predict what would occur in the breakability assessment study, regarding inequity of both halves after splitting.

In **Table 19** it is presented, in percentage, the mass deviations from the previous established average tablet weight (second column in **Table 6**), both from the results during the assessment of mass uniformity (that occurred in a laboratory from the faculty) as the results during the breakability assessment study (that occurred in the community pharmacy). In the first study only one subject broke all the tablets, with only two different methods. In the case of flat tablets, the subject held the tablet between fingers and applied pressure downwards. In the case of convex tablets, the subject applied pressure downwards, pushing towards a surface with only the aid of thumbs. In the second study, a total of 47 different volunteers broke different tablets, with no indication of the method they should use (only that they could only use their hands, with no mechanical assistance (13)), therefore a few of methods were applied to subdivide the tablets. Given these facts, some differences were expected to occur regarding the accuracy of subdivision.

A comparison between the columns of **Table 19** regarding the halves can be done to predict which of the tablets would have a less accurate subdivision. For example, looking at the results of the halves (mass uniformity results):

a) tablet 011109 presents a deviation of 47,73% (Halve B), which means less 2,27% of mass than what it was expected;
b) tablet 021220 presents a deviation of 46,91% (Halve B), which means less 3,09% of mass than what it was expected;
c) and tablet 121119 presents a deviation of 44,96% (Halve A), which means less 5,04% of mass than what it was expected.

These are important findings because even if the sum of the halves do not have a representative mass loss, the halves do, and therefore a discrepancy in content in terms of the active substance can occur, therefore causing dose fluctuations for the patient. Now looking at the results of the halves (breakability assessment test), tablet 101102 presents deviations of 49,4% (Halves A) and 46,3% (Halves B). Not only does the 46,3% value represent a mass loss of 3,7% of that halve, but also the sum of these percentages represent a total of 4,4% of total mass loss. This fact is consistent

with the results in **Table 13** since tablet 101102 was the tablet presented most of the cases where the tablet broke in more than two fragments (instead of two halves).

It is also interesting to see that the three tablets that suffered less variation (021010, 021118 and 021220, in decreasing order) in the mass uniformity assessment are the same as in the faculty (021118, 021220 and 021010, in decreasing order).

Since the products that were provided for the study were generic products, a research was done in order to find out to detect any discrepancies between the SmPC and PIL of these generic products and the SmPC and PIL of the reference drug. This was proven to be true since some reference drugs presented score lines with a different purpose than the generic product, which should not occur since they should present consistent scoring purposes. In second place, the product leaflets that came with the provided boxes - which were all within the expiration date - did not match the majority of the online documents (19), which means that updates to the SmPC and the PIL were made but products are commercialized with outdated information. Also, in some cases, differences regarding the purpose of the score line were detected between the SmPC and the PIL, which suggests that sometimes patients do not get the same information about the suitability of the score line as healthcare professionals do.

Moreover, concerning labelling, the intended function of score lines should be stated in the SmPC or the (PIL), e.g. the mentioning of "functional scoring" (1) as well as the intended dose after splitting, because basing that interpretation on posology schemes might be subjective. Also, there should not be misleading characteristics (e.g. bisected (1)). It is purposed that standard quotes are included in the labelling ("The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.", "The tablet can be divided into equal halves." and "The tablet should not be divided." (15)). A pictorial information regarding the method that is advised to split the tablet should also be included in labelling (as shown in **Figure 1**, retrieved from (10)). Finally, there should be a concern about transmitting information regarding storage conditions after splitting (e.g. the period of time that ensures safety of the split tablets and atmospheric conditions).

Since some discrepancies can occur between the content of each halve of tablets after they are split, assessments should ensure safety regarding the subdivision of tablets, based on aspects of subdivision of tablets should be assessed, namely the "accuracy of subdivision", "loss of mass" and the "ease of subdivision" (as advised in) (5). These assessments should be done not only on the pharmaceutical

development (e.g. manufacturing scale-up processes, changes regarding excipients changes) but also in validation of product batches.

6 Conclusion

The present study has examined if products marketed in Portugal are in compliance with regulatory requirements, regarding the subdivision of tablets.

A comprehensive review was made regarding regulatory requirements and available guidance documents concerning this subject, published in the last seventeen years. Even though a lot of important concerns have been raised, not all of them are actually implemented in a mandatory and legal manner. This is considered to be of extreme relevance since more strict criteria would allow less non conformities, and therefore more safety for the patient regarding the usage of scored tablets. For instance, in this study, 10,22% of the observations reflect either the inability of the volunteers to break the tablets or the splitting of tablets in more fragments than the two expected halves.

Further findings of this study showed that around half of the observations correspond to situations in which the patients classified the tablets as very easy to break. However, a fifth of the observations represent situations where the patients found the tablets hard or very hard to break as well as cases where the patient was not able to break the tablet.

The usage of a prediction models showed to be a valuable asset in order to determine which tablet physical and pharmacotechnic parameters should be optimized for an enhanced and accurate tablet subdivision.

New pharmaceutical approaches could be explored to minimize the effects of inaccurate tablet splitting, for instance, providing individual tablet cutters with the medicines or the usage of illustrations in product labelling to ensure an easy and even subdivision, as well as more information about the purpose of the score line

A limitation of this study was that the provided products to do the assessments might not represent the overall variety of marketed tablets with score lines. Furthermore, it would be interesting to compare reference drugs instead of only

generic products. However, the findings of the breakability assessment study that was done have brought “real world testing” evidence to this matter.

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